Mass Spectrometry 2017: Heterocyclic aromatic amines and their contribution to the bacterial mutagenicity of the particulate phase of cigarette smoke - Regina Stabbert - University of Cologne

ABSTRACT

Since the detection of substances with very high bacterial mutagenicity in cooked/broiled meat and fish and their identification as heterocyclic aromatic amines (HAAs), this class of compounds has initiated extensive research that is still ongoing. HAAs are formed typically at higher temperatures (140–165 C) as the result of Maillard reactions involving creatinine, free amino acids (espe- cially tryptophan and glutamic acid), and sugars (Wakabayashi et al., 1993). Special attention is given in the literature to the following carboline type of HAAs: MeAaC, AaC, Trp-P-1, Trp-P-2, Glu-P-1, Glu-P-2, and the aminoimidazo type of HAAs: IQ, MelQ, MelQx, PhlP. Harman and norharman, although b-carbolines, are not considered as member of the HAA class in most publications as they lack an exocyclic amine group. The exocyclic amine group of HAAs can undergo metabolic activation by N-hydroxylation producing an intermediate (arylnitrenium ion) which has been implicated in general toxicity and DNA damage (Turesky and Le Marchand, 2011 With the exception of harman and norharman, the mentioned HAAs exhibit a clear in vitro activity inducing reverse mutations in Salmonella typhimurium (Ames assay), morphological transforma- tion in mouse fibroblasts, micronucleus induction in human cells, and DNA strand breaks (Comet Assay) in human cells and genotoxic effects in vivo as DNA adducts (Arimoto-Kobayashi et al., 2006; Dingley et al., 2003). Micronuclei formation could be demonstrated for PhlP in mice but not for MelQ and IQ (Durling and Abramsson-Zetterberg, 2005). The carcinogenicity of PhlP, MelQ, and IQ in mice and rats in various organs, like liver, pancreas, colon, mammary gland, and prostate is well established at doses around 10 mg/kg/day. Carcinogenicity studies in nonhuman primates with PhlP, MelQ, and IQ could only demonstrate a carcinogenic action of IQ in the liver at doses of 10 and 20 mg/kg/day (Takayama et al., 2008). Differences in metabolism between rodents and primates account for the observed differences in the carcinogenic effects.

In humans, no occupational exposures to pure HAAs have been reported. However, since the detection of HAAs in food, there are concerns that their presence in food might cause tumors in men.Several epidemiological studies have tried to find an association between the intake of, e.g., cooked meat, cooked fish, or fried potatoes and several tumor types, especially those of the colon (WCRF/AICR,1997). These studies are mainly based on questionnaires exploring the diet of the participants. For colorectal adenomas or carcinomas there are more studies that showed an association (although not always statistically significant) than those that gave a negative result (Kim et al., 2013; Berlau et al., 2004). Associations between HAAs and tumors at other sites are in summary even more inconclusive. Considering these uncertainties, insufficient evi- dence exists to establish a definite conclusion on the role of HAAs in the genesis of human tumors. This conclusion is consistent with the assessments of the International Agency for Research on Cancer that has not listed any of the HAAs as a definite human carcinogen (IARC, 2015); IQ was classified as a

'probable human carcinogen'(Group 2A) and other assessed HAAs (AaC, Glu-P-1, Glu-P-2, MeAaC, MelQ, MelQx, Trp-P-1, Trp-P-2) as 'possible human carcinogens' (Group 2B). Comparing the doses that gave rise to a distinct tumor development in rodents and monkeys with the estimated daily oral intake of HAAs by humans shows that the estimated human exposure is more than 1000 times lower. As such, a not yet identified mechanism would be needed to explain a link between HAAs and human tumorigenicity (Wakabayashi et al., 1993).Maillard reactions are well-known to occur in the burning cigarette and as all components necessary to form HAAs are present in tobacco, it has been suggested that HAAs should also be found in cigarette smoke. Three years after the initial studies of Sugimura et al. at the National Cancer Center Research Institute in Japan where HAAs in the diet could be identified the first HAAs, AaC and MeAaC, were identified and quantified in TPM of cigarette smoke . Further studies by several different laboratories using different analytical methodologies identified additional HAAs in TPM

Despite some concerns regarding the biological activity of HAAs in TPM, it was only in 1997 that several HAAs were included in a revised list of "[c]arcinogens in tobacco and cigarette smoke" issued by Hoffmann and Hoffmann (1997). More recently, the U.S. Food and Drug Administration (FDA) has included 8 HAAs in their list of 93 'Harmful and Potentially Harmful Constituents (HPHCs) in tobacco products and tobacco smoke' (FDA, 2012). A more recent list of 39 priority toxic contents and emissions of tobacco products does not include HAAs (WHO, 2015).

As data on the mutagenicity of HAAs in the context of TPM are scarce and, regarding interactions, nearly non-existent, the research presented here was targeted to corroborate the existing potency data on single HAAs, their occurrence in TPM, their contribution to the overall mutagenicity of TPM, and their interactions with TPM or between the HAAs themselves. Hereby, an improved analytical method for the quantification of the HAAs in TPM was applied.

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